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Formulation and Evaluation of Floating Tablets of Atazanavir:

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Abstract: The main aim of this research work on hydro-dynamical drug systems is to develop the Atazanavir controlled release tablets using floating technique to estimate the gastric retention time and the release kinetics with sustain release tablets and furthermore to keep up constant therapeutic effect of the drug for more than 12 hrs. The weight of atazanavir was settled as 400 mg and the aggregate weight of the tablet was considered as 600 mg. The polymers xanthan gum, karaya gum, guar gum, and carbopol were of 15, 30, 45 and 60 mg. From the dissolution studies conducted it was evident that the formulation (F14) showed better and desired drug release pattern i.e., 98.54 % in 12 hours. The drug followed zero order release kinetics with super case II mechanism.

Keywords: Atazanavir, Xanthan gum, guar gum, karaya gum, carbapol, floating tablets.

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I. INTRODUCTION:

The gastro retentive drug delivery has the ability of retaining the drug in the Gastro-intestinal tract (mainly stomach) for a very long duration. In the marketing of a new drug entity complications have increased rapidly, therefore, a significant attention was focused on development of sustained or a controlled release drug delivery system.

The main goal in designing a controlled and sustained drug release system is to reduce dosing frequency or increase the drug effectiveness by localization of the target site and thus providing a uniform drug delivery [1].

A few limitations in the oral drug delivery system took way to the gastro-retentive drug delivery systems (GRDDS). In addition to continuous drug delivery to the small digestive tract, a couple of benefits given from GRDDS include: -

a) A therapeutic effect for prolong time is achieved.
b) A lessening in the recurrence of drug dosing
c) A powerful treatment for the nearby stomach disorders.[2]

However, the development process is limited by several physiological difficulties, which include the inability to localize the drug delivery system (DDS) within the desired regions of the gastrointestinal tract (GIT) and the highly varying nature of gastric emptying process.

It can be predicted that, depending on the physiological state of the subject and the design of the pharmaceutical formulation, emptying process lasts for a few minutes to 12hours.

This fluctuation, may prompt uncertain bioavailability and times to accomplish peak plasma levels, since the vast majority of the medications are specially caught up in the upper part of the small digestive tract.[3]

FLOATING DRUG DELIVERY SYSTEMS: They are the low-density systems that have sufficient buoyancy to float over the gastric contents and are buoyant in the stomach without altering the gastric emptying rate for a prolonged length of time. As the system was floating on the gastric contents, the medicament was released slowly at a specific rate from the drug system. After that release from the stomach emptying of the residual system is done. A number of buoyant systems have been developed based on tablets, granules, powders, capsules, laminated films and hollow microspheres.[4]

Ideal drug candidates for floating drug delivery:

A) Drugs those are locally active in the stomach. Eg. Misoprostol, antacids etc.
B) Drugs which have narrow absorption window in the GIT. Eg. Furosemide, L-dopa, Para-amino benzoic acid, riboflavin.etc.

C) Drugs that exhibit low solubility at high pH values. Eg. Diazepam, Chlordiazepoxide, Verapamil hydrochloride.
D) Drugs those are unstable in the intestinal or colonic environment. E.g. Captopril, ranitidine HCl, Metronidazole.
E) Drugs that disturb normal colonic microbes. E.g. antibiotics against Helicobacter pylori.Drugs having a specific site of absorption in the upper part of small intestine.
F) Drugs having a bulk density of less than 1 to remain in the stomach for a prolonged period of time.[5]

FACTORS AFFECTING GASTRIC RETENTION:

The various factors which effect the gastric retention time of floating tablets cab be given as follows:

a. Density
b. Size
c. Shape of the dose system:
d. Single and numerous unit definitions
e. Fed or unfed state
f. Nature of food
g. Caloric substance of food
h. Re-ocurrence of feed
i. Sex
j. Age
k. Posture
l. Concomit administration of drug
m. Biological components

APPROACHES TO GASTRIC RETENTION:

Various methodologies have been utilized to build the GRT of a drug form in stomach by utilizing an assortment of ideas.

1. Floating systems
2. Bio mucoadhesive systems
3. Receptor- mediated adhesion
4. Swelling/Expanding systems
5. Super porous hydrogel systems
6. Magnetic systems
7. High-density systems
8. Raft systems[6]

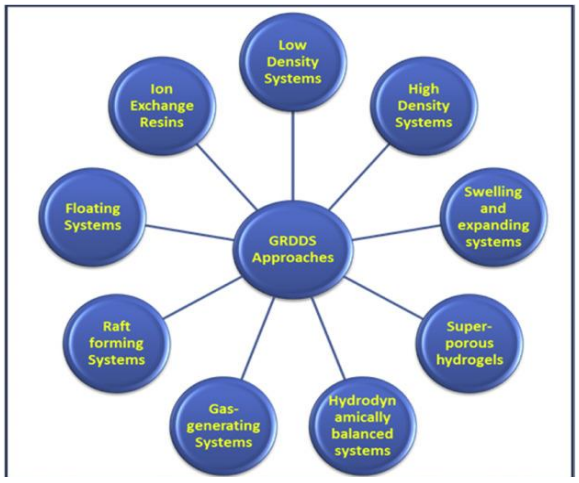


Figure no.1: Various techniques of gastro retentive drug delivery systems.

1) Floating Systems:

1) Floating Systems: These systems (FDDS) have a bulk density lower than that of the gastric liquids and in this way, stay light in the stomach for longer time, without influencing the gastric emptying rate. In the interim, the drug/drug system is coasting on the gastric substance, the medication is discharged at a specific rate from the

floating drug system. This outcomes in an expansion in the GRT and significantly more decreased changes in the plasma sedate focuses.[7]

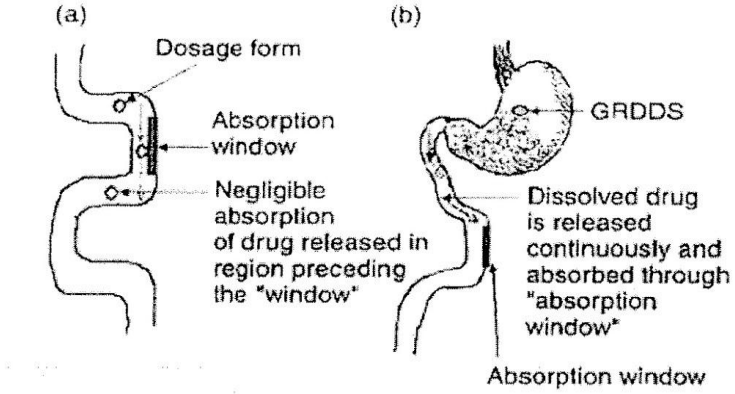


Figure no.2: Drug absorption in the case of
(a) Conventional dosage forms
(b) GRDDS

a) Effervescent system:
These systems create gas (CO2), there by diminishing the density of the system, and stays light in the stomach for a drawn out time frame and discharge the medication consistently at a desired rate. It mainly comprises of the swellable polymers like chitosan, methylcellulose and foaming mixes, for example, citric acid, tartaric acid, sodium bicarbonate.11
The effervescent floating drug delivery systems generate gas (CO_2), thereby reducing the density of the system, and helps to remain buoyant in the stomach for a prolonged period of time and release the drug steadily at a desired rate. The effervescent system mainly consists of the swellable polymers like chitosan, methylcellulose and effervescent compounds such as citric acid, tartaric acid, sodium bicarbonate.[8]

b) Non-effervescent systems
Upon organization, they swell over the top by means of imbibitions of gastric liquid to a degree that it keeps their exit from the stomach. Such drug/drug systems might be alluded to as the "plug-type systems‟ since they tend to remain logged close to the pyloric sphincter.
Colloidal gels, alginate dabs, Microspheres and microporous compartment system are couple of cases for this sort of dose forms.[9]

a. Single Layer Floating Tablets:
These single layer tablets were planned by suggest blending of medication with a gel-framing hydro colloid, which swells in contact with gastric liquid and keeps up a bulk density of not as much as one.
The air which is caught by swollen polymer gives the buoyancy to these medicaments.[10]

b. Bilayer Floating Tablets: A bilayer tablet contains two layers i) with prompt discharge layer which discharges an underlying dosage from drug/drug system ii) a sustain discharge layer that retains gastric liquid, shaping an impermeable colloidal gel boundary on its surface, and in this manner keep up a bulk density of not as much as that of single unit and along these lines it stays buoyant inside.

c. Alignate Beads: The multi-unit floating dose forms were created from the freeze-dried calcium alginate beads. Circular beads of roughly 2.5 mm distance across are set up by dropping the sodium alginate arrangement into watery arrangement of calcium chloride and with continuous precipitation of calcium alginate prompting development of porous system. It can keep up a floating force for more than 12hours. At the point when contrasted and strong beads, which gave a brief timeframe of residence1 hour, and these floating beads gave a drawn out residence time of over 5.5 hours.[11]

d. Hollow Microspheres:
The microspheres were stacked with medicament in their external polymer shells and in turn formulation was carried out by an emulsion-dissolvable dispersion technique. An ethanol: dichloromethane arrangement of medication and an enteric acrylic polymer was discharged into a disturbed watery arrangement of PVA that was

thermally controlled at 400C. The gas stage created in scattered polymer bead by dissipation of dichloromethane has shaped an interior hole in microsphere of polymer alongside medicate.
These microspheres coasted consistently finished the surface of acidic disintegration media containing surfactant for over 12 hours in – vitro.[12]

2. Bio Mucoadhesive systems Bioadhesive medication systems are utilized as a delivery gadget inside the lumen to improve drug retention in a site particular manner. This approach includes the utilization of the bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Probably the most encouraging excipients that have been utilized ordinarily in these incorporate lectins, carbopol, chitosan etc.[13]

a. Hydration-mediated adhesion: Certain hydrophilic polymers tend to imbibe large amount of water and become sticky and therefore acquire bioadhesive properties.

b. Bonding-mediated adhesion: The connection of polymers to a bodily fluid or epithelial cell surface includes many bonding mechanisms, including a synthetic bond and physical-mechanical holding. Physical-mechanical bonds are the after effects of addition of the sticky material into fissure or creases of the mucosa. Though synthetic bonds might be either covalent (essential) or ionic (optional) in nature. The chemical bonds comprise of dispersive connections like Vander Waals associations and more grounded particular collaborations, for example, hydrogen bonds. Hydroxyl and carboxylic groups are in charge of development of hydrogen bonds.[14]

3. Receptor-mediated adhesion: Certain polymers can tie to particular receptors it is on the cell surfaces, thereby improving the gastric maintenance time of medication forms. A couple of plant lectins, for example, tomato lectins cooperate particularly with the sugar bunches introduce in the bodily fluid or on the glycocalyx.[15]

4. Swelling/ Expanding Systems: This class of gastro retentive works are suitable for swelling in stomach. The extended structure is caught in the stomach for a drawn out time frame prompting maintained medication discharge and a controlled retention in stomach and furthermore digestive system. Such systems are regulated per-orally as capsule bearing the measurement shape in collapsed and minimized arrangement. At the point when presented to gastric condition the case shell break sand the dose shape achieves its extended structure, which is held in stomach for longer time. Easy formulation, straight forward in operation and reproducible outcomes are advantages of this drug system, they experience the ill effects of disadvantage like stopping up of pylorus end of stomach.

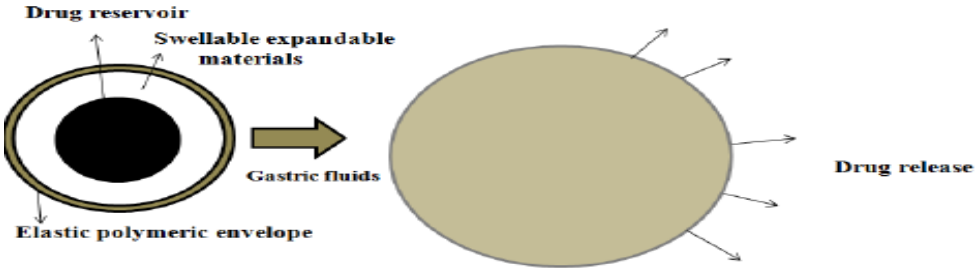


Fig no.3: Drug release from swellable system

5. Super porous hydrogel systems: These swellable units contrast adequately from the coventional sorts to warrant.
Isolate grouping. In this way to deal with enhance GRT super permeable hydrogels of normal pore estimate >100 micromiter, swell to harmony measure inside a moment because of fast water take-up by fine wetting through various interconnected open pores. They swell to a huge size (swelling proportion: at least 100) and are proposed to have adequate mechanical quality to withstand weight by gastric constriction. This is instructed by co-detailing with respect to hydrophilic particulate material.[16]

6. Magnetic Systems: This way to deal with improve the gastric retention time (GRT) depends on the basic rule that the dose form contains a little inward magnet, and a magnet put on the mid-region of abdomen. Even though it appears to work, the outer magnet must be situated with a level of exactness that may bargain patient compliance.

7. High-density systems: Essentially, gastric substance have a mass near to water (¨1.004gcm-3). At the point when the patient is upright little high-density pellets sink to the base of the stomach, where they move toward

becoming entrapped in the folds of the antrum and withstand the peristaltic rushes of the stomach divider. A density near 2.5 g cm-3 appears to be important for noteworthy prolongation of gastric residence time and barium sulfate, zinc oxide, press powder, titanium dioxide are utilized as excipients.[17]

8. Raft systems: These system have got much consideration for the delivery of antacids in stomach and medication conveyance for gastro intestinal contaminations and other disorders. The instrument engaged with the raft arrangement incorporates the development of a cohesive gel in contact with gastric liquids, where in each part of the fluid swells shaping a constant layer called a pontoon. This raft glides on gastric liquid due to the low mass density made by the arrangement of CO2. For the most part, the drug/drug system contains a gel shaping specialist and basic bicarbonates or carbonates in charge of the arrangement of CO2 to make the drug/drug system less thick and ready to float on the gastric liquids.[18]

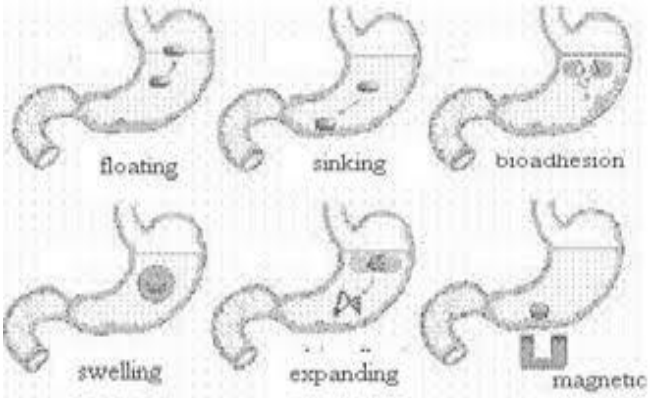


Figure no.4 Drug release pattern in various types of GRDDS

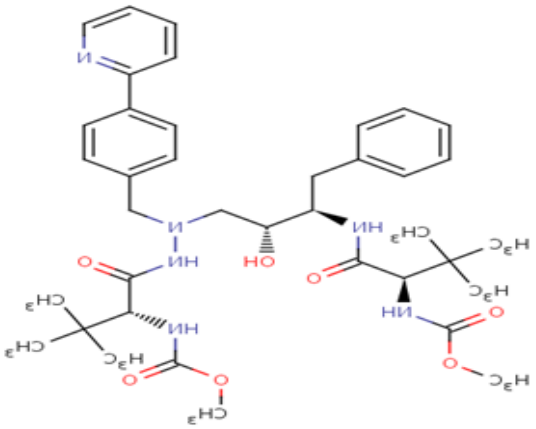
II. MATERIALS AND METHODS:

Table no.1 Materials used for preparation of floating tablets of atazanavir:

Sr. No.	Materials used	Grade	Supplier
1.	Atazanavir	Pharma grade	Cipla pharmaceuticals limited pvt ltd., Mumbai.
2.	Karaya gum	LR	Spectrum Pharma labs Hyderabad
3.	Guar gum	LR	Spectrum Pharma labs Hyderabad
4.	Xanthan gum	LR	Shreeji chemicals, Mumbai
5.	Carbopol	LR	Shreeji chemicals, Mumbai
6.	Avicel	LR	S.D fine chemicals, Mumbai
7.	Sodium bicarbonate	LR	S.D fine chemicals, Mumbai
8.	Lactose	LR	Shreeji chemicals, Mumbai
9.	Mg-Stearate	LR	Shreeji chemicals, Mumbai
10.	Talc	LR	Shreeji chemicals, Mumbai
11.	Hydrochloricacid	LR	Center drug house (p) Ltd, Mumbai

Drug: Atazanavir
Proprietatry name: Latazanavir, Reyataz, Zrivada
Chemical name:
methyl-N-[(1S)-1-{N'-[(2S,3S)-2-hydroxy-3-[(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanamido]-4-phenylbutyl]-N'-{[4-(pyridin-2-yl)phenyl]methyl}hydrazinecarbonyl}-2,2-dimethylpropyl]carbamate.
Empirical formula: C38H52N6O7
Molecular weight: 704.856 g/mol

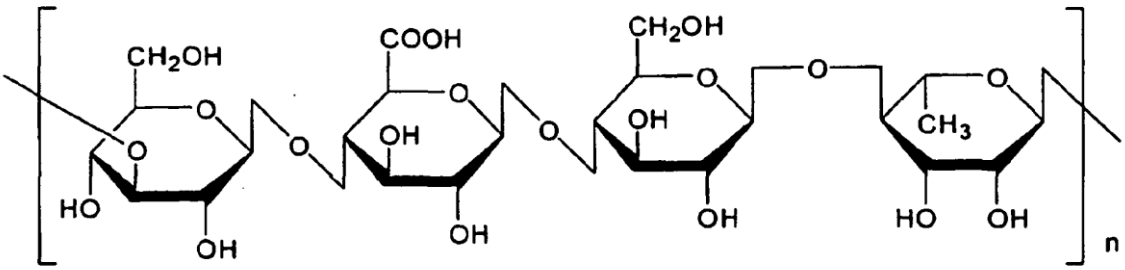
Structure:



PHYSICOCHEMICAL PROFILE:
Description: It is a white to pale yellow crystalline powder .
Solubility: Drug is freely soluble in water and methanol.

PHARMACEUTICAL PROFILE:
Dosage Forms and dose: 100mg, 150mg, 200mg, 300mg capsules.
Pharmacopoeial status: United States Pharmacopoeia
ANALYTICAL PROFILE
Spectrophotometry: The spectrophotometric determination of Atazanavir in methanol with the λmax at 279nm has been reported.[19]
PHARMACOKINETIC PROFILE:
Oral absorption: 60-68%.
Plasma half life: 5-7 hours.
Protein binding: 86 %
Pharmacological Profile: Therapeutical category: ANTI HIV
MECHANISM OF ACTION: Atazanavir, which is an azapeptide, is a specific, reversible HIV-1 protease inhibitor. It works by restraining the cleavage of viral Gag and Gag-Pol polyprotein antecedents into individual useful proteins, keeping the preparing of the polyproteins into develop and irresistible virions. Atazanavir is an idle against HIV-2.[20]

EXCIEPIENTS:
KARAYA GUM:
Synonyms: Karaya, gum karaya, Kadaya, gum sterculia, Katilo, Kuterra, Sterculia,;
Structure:

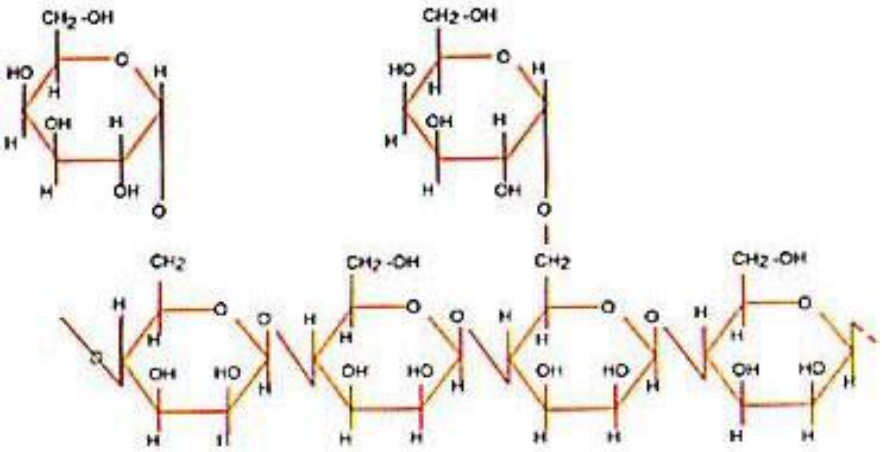


Low Acyl form

Functional uses: Emulsifier, stabilizer, thickening agent
Swelling by ethanol arrangement: Karaya gum swells in 60% ethanolin order to recognize it from different Gums.[21]

GUAR GUM:
Synonyms: E412; Galactosol;guarflour; jaguargum; Meyprogat; Meyprodor; Meyprofin.
Functional category: Suspending agent; tablet disintegrant; viscosity increasing agent and also tablet binder.[22]

Chemical Structure of Guar Gum

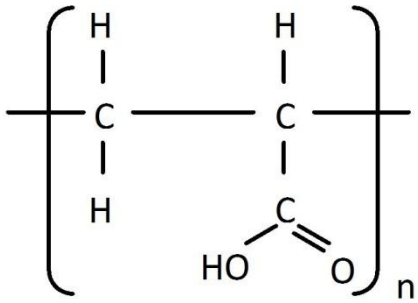


XANTHAN GUM

Synonyms: Corn sugar gum; Merezan; Rhodigel.
Functional category: Stabilizing, suspending and viscosity building agent.[22]

CARBOPOL934P:

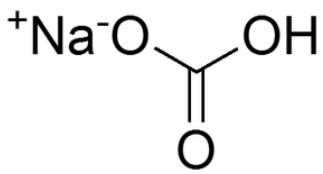
Synonyms: Acritamer, acrylic acid polymer carboxy vinyl polymer.
Empirical formula : $(C_3H_4O_2)_x(\text{-}C_3H_5\text{-sucrose})_y$
Structure:



Category: Bioadhesive, Emulsifying, suspending & viscosity enhancing agent, Tablet binder and release-modifying agent.[23]

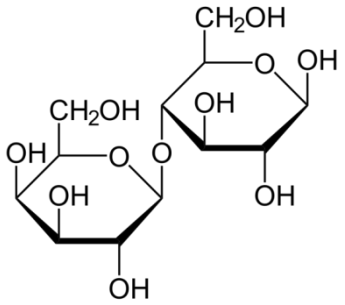
SODIUM BICARBONATE

Synonyms: Baking soda; sodium acid carbonate; sodium hydrogen carbonate.
Empirical Formula and Molecular Weight: $NaHCO_3$ 84.01
Structure:



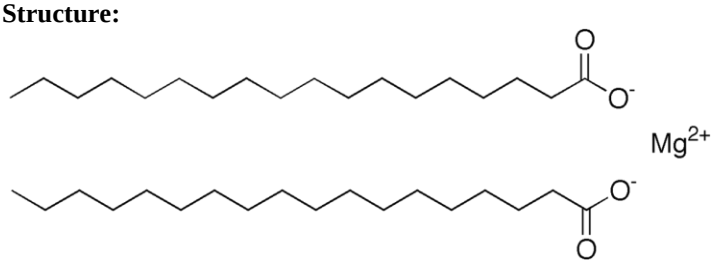
Functional Category: Alkalizing agent; therapeutic agent.[24]

LACTOSE
Synonym: Fast-flo.Lactochem, Microtose, Milksugar, pharmatose, succharumlactis, Tabletose, Zeparox.



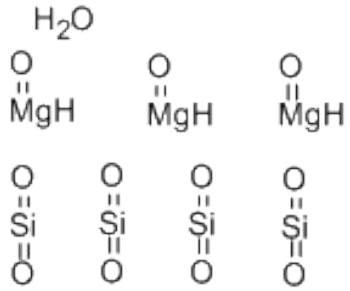
Structure:
Functional category: Tablet and capsule diluent.
Application: Widely used as a filler or diluent in tablets and Capsules.[25]

MAGNESIUM STEARATE
Synonyms: *HyQual*, magnesium octa-decanoate, stearic acid magnesium salt.
Structure:



Functional category: Tablet and capsule lubricant.
Applications: It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0 %.[26]

TALC
Synonyms: Altalc; E553b; hydrous magnesium calcium silicate; LuzenacPharma; hydrous magnesium silicate; magnesium hydrogen metasilicate; Magsil Star; powdered talc; purified French chalk; soapstone; Magsil Osmanthus; steatite; Superiore.
Structural Formula: $Mg_6(Si_2O_5)_4(OH)_4$.



Functional Category: Anticaking agent; glidant; tablet and capsule lubricant.[27]

Methods:
Determination of melting point:
The MP of Atazanavir was controlled by capillary method. Fine powder of Atazanavir was filled in glass tube (already fixed toward one side) and then tube is connected to the thermometer and put in an oil bath (light paraffin oil). The temperature at which it begins to liquefy was noted.

Determination of λ max of Atazanavir utilizing 0.1 N HCL:
A solution of Atazanavir containing the fixation 10µg/ml was set up in 0.1N HCL and UV range was taken. The arrangement was filtered in the scope of 200-400nm.

Standard calibration curve of Atazanavir utilizing 0.1 N HCL:
Method: 10mg of medication was precisely in 10ml of volumetric jar. It was broken up into 0.1N HCL to give

1000µg/ml. the standard stock arrangement was then serially weakened with 0.1N HCL to get 1to10µg/ml of Atazanavir. The absorbance was measured against 0.1N HCL as clear utilizing the UV spectrophotometer. The absorbance esteems were plotted against drug concentration (µg/ml) to acquire the standard calibration curve.[28]

Compatibility:
These studies were performed through FTIR spectroscopy. The IR range of unadulterated medication and physical blend of medication and polymer was considered. The absorption peaks of Atazanavir were achieved at 4000-500cm-1.[29]

Pre-compression parameters:
a) Angle of repose
b) Bulk density
c) Tapped density
d) Carr's compressibility index
e) Hausner's ratio

PREPARATION OF ATAZANAVIR FLOATING TABLETS:
BY DIRECT COMPRESSION METHOD:
Atazanavir floating tablets were set up by direct compression procedure utilizing medication and variable centralization of polymers (karaya gum, guar gum, MCC,carbopol, Sodium Bicarbonate, Lactose, xanthan gum, talc and Magnesium sterate).

The individual powders and other excipients were mixed completely with the utilization of a mortar and pestle. The powder mixed was then greased up with Mg-stearate and powdered and after that compacted on a tablet punching machine.[29]

Post-compression parameters:
a) Weight variation
b) Friability
c) Hardness
d) Drug content uniformity
e) Diameter and thickness
f) Dissolution studies
g) In-vitro buoyancy studies
h) Swelling studies[30]

III. RESULTS:

Determinationof melting point: The MP of Atazanavir was controlled by capillary method. Fine powder of Atazanavir was filled in glass tube (already fixed toward one side) and then tube is connected to the thermometer and put in an oil bath (light paraffin oil). The temperature at which it begins to liquefy was noted.
Themeltingpointof Atazanavir wasfound to be in rangeof **209 °C**

ESTIMATION OFATAZANAVIR BY UV SPECTROSCOPY:
Method: A solution of Atazanavir containing the fixation 10µg/ml was set up in 0.1N HCL and UV range was taken. The arrangement was filtered in the scope of 200-400nm.
UV Spectra ofAtazanavir at10µg/ml concentration.
Wavelength of maximumabsorption in 0.1N HCLsolution was found to be**279nm.**

CALIBRATIONCURVE:
Standard calibration curve of Atazanavir utilizing 0.1 N HCL:
Method: 10mg of medication was precisely in 10ml of volumetric jar. It was broken up into 0.1N HCL to give 1000µg/ml. the standard stock arrangement wast then serially weakened with 0.1N HCL to get 1to10µg/ml of Atazanavir. The absorbance was measured against 0.1N HCL as clear utilizing the UV spectrophotometer. The absorbance esteems were plotted against drug concentration (µg/ml) to acquire the standard calibration curve.

Table no.2: Absorbancedata forthe calibration curveofAtazanavir in 0.1N HCL

Concentration Concentration(µg/ml)	**Absorbance**
0	0
5	0.066
10	0.12
15	0.191
20	0.249
25	0.315
30	0.381

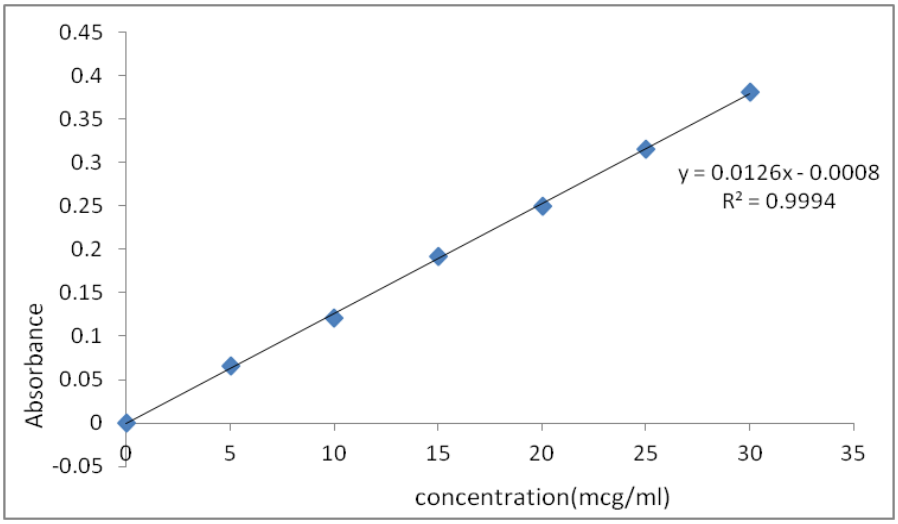


Figure no.5: Standard calibration curveofAtazanavir in 0.1NHCl

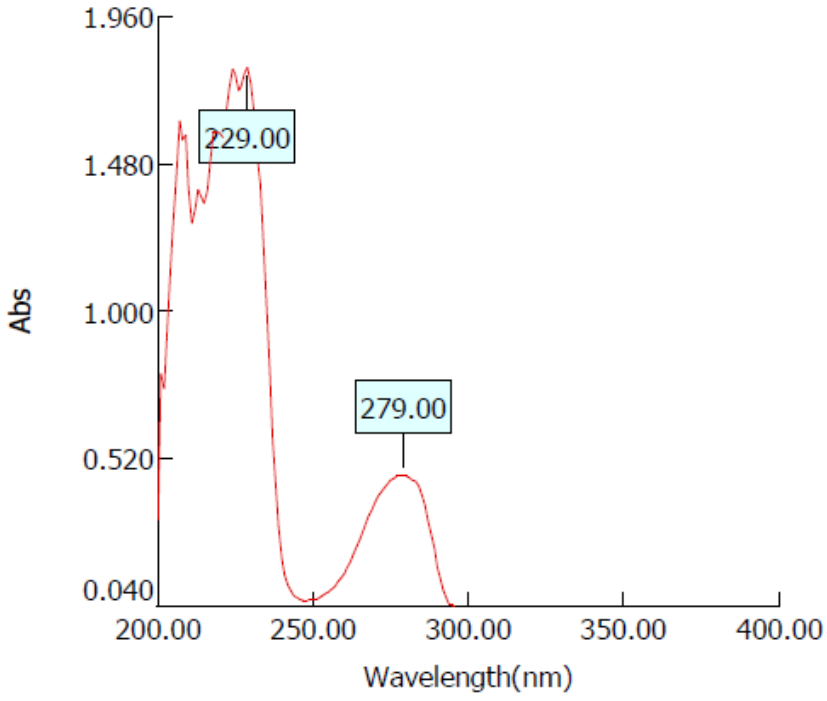


Figure no.6: Uv Spectrum Of Atazanavir 279 nm

COMPATABILITY STUDIES

FTIR Spectroscopy

IdentificationofAtazanavir: TheIRspectrumofpuredrugwasfoundtobesimilartothestandardspectrum ofAtazanavir.

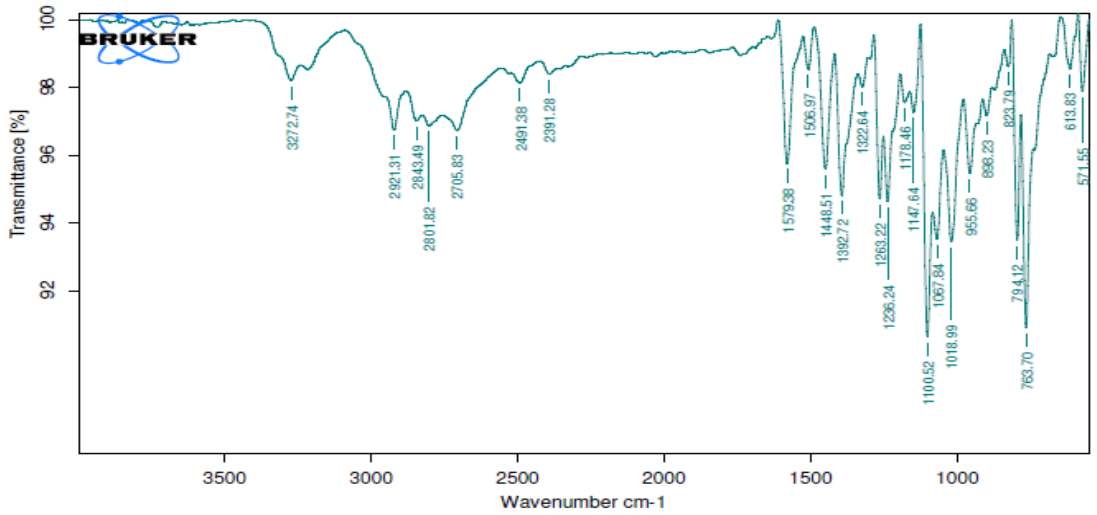


Figure no.7: IRspectraof Atazanavir

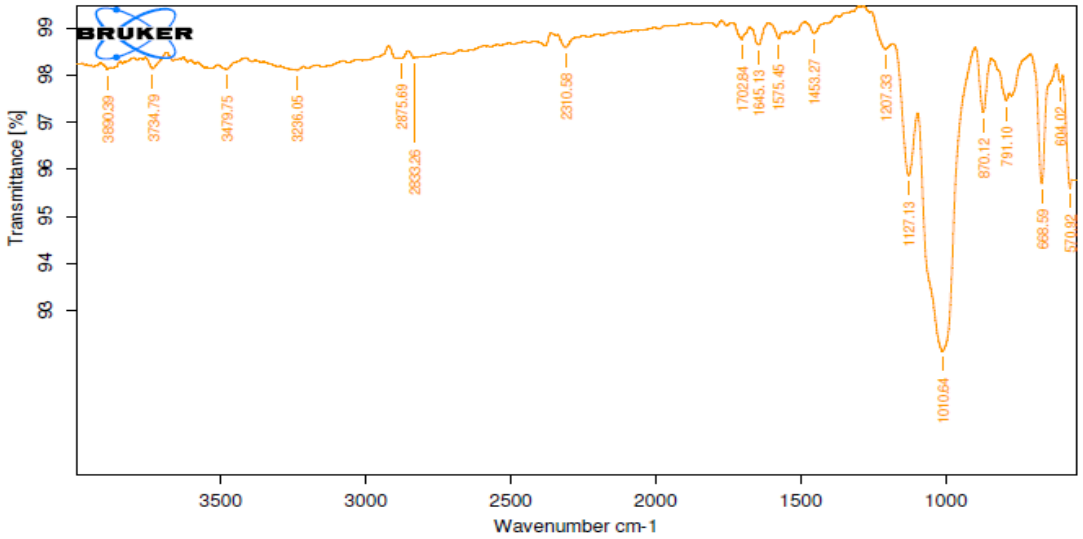


Figure no.8:FT-IR Spectraof Atazanavir optimized formulation

PRE-COMPRESSION EVALUATIONOFATAZANAVIRFLOATINGTABLETS

Table no.3: Pre-compression parameters of Atazanavir floatingtablets

Formulation code	Angleof repose (θ)±SD	Bulk density (gm/cm)	Tapped density (gm/cm)	Hausner ratio (HR)±SD	Carrindex (CI)±SD
F1	22.21±0.825	0.224±0.010	0.262±0.011	1.169±0.006	14.503±0.521
F2	21.84±0.214	0.210±0.010	0.250±0.010	1.190±0.010	15.398±0.594
F3	22.96±0.325	0.227±0.010	0.266±0.005	1.101±0.005	14.662±0328.
F4	22.85±0.486	0.230±0.010	0.270±0.018	1.173±0.010	14.817±0.550
F5	22.46±0.518	0.225±0.020	0.260±0.010	1.150±0.060	13.462±0.357
F6	22.64±0.728	0.234±0.015	0.270±0.026	1.153±0.010	13.336±0.640
F7	23.64±0.318	0.220±0.005	0.252±0.011	1.457±0.004	12.696±0.732

F8	22.85±0.625	0.230±0.011	0.260±0.010	1.124±0.005	11.539±0.592
F9	21.54±0.289	0.220±0.010	0.266±0.015	1.130±0.010	17.297±0.594
F10	22.21±0.825	0.224±0.010	0.262±0.012	1.169±0.006	14.503±0.521
F11	22.85±0.520	0.230±0.010	0.270±0.010	1.173±0.010	14.817±0.550
F12	23.64±0.312	0.220±0.005	0.262±0.019	1.190±0.004	16.036±0.732
F13	21.54±0.346	0.220±0.010	0.266±0.019	1.219±0.010	17.293±0.594
F14	22.21±0.818	0.224±0.020	0.262±0.014	1.169±0.006	14.503±0.508
F15	22.21±0.816	0.222±0.018	0.252±0.012	1.164±0.006	11.904±0.411
F16	24.21±0.824	0.224±0.012	0.268±0.012	1.162±0.002	14.523±0.518

All thevalues are expressed as mean± SD. (n=3)

POST COMPRESSION EVALUATIONOF ATAZANAVIR FLOATINGTABLETS:

Table no.4: Post-compression evaluation of Atazanavir floatingtablets

Formulation code	**Weigt variation Average wt in (mg)±SD**	**Hardness (Kg/cm^2) ±SD**	**Diameter in(mm) ±SD**	**Density in(mm) ±SD**	**Friability (%)±SD**	**Drug content uniformity (%)±SD**
F1	580.2±0.95	4.932±0.10	8.57±0.57	4.129±0.01	0.736±0.09	96.362±0.30
F2	601.97±0.87	4.863±0.10	9.00±0.02	4.239±0.04	0.745±0.06	98.738±0.22
F3	599.1±0.85	4.946±0.15	8.15±0.17	4.653±0.01	0.729±0.01	98.432±0.35
F4	598.14±0.81	4.644±0.11	9.10±0.000	4.204±0.10	0.663±0.01	94.513±0.13
F5	600.5±0.84	4.943±0.12	9.18±0.57	3.144±0.06	0.562±0.05	97.564±0.40
F6	597.6±0.86	4.856±0.11	9.55±0.27	4.126±0.05	0.739±0.01	99.244±0.81
F7	598.15±0.81	4.737±0.15	8.45±0.22	4.942±0.05	0.623±0.01	98.424±0.11
F8	600.04±0.85	4.802±0.20	8.67±0.46	4.355±0.10	0.722±0.01	96.172±0.67
F9	596.12±0.70	4.355±0.28	9.34±0.21	4.245±0.057	0.716±0.05	99.072±0.61
F10	600.2±0.92	4.932±0.15	8.67±0.37	4.129±0.02	0.706±0.09	96.122±0.30
F11	600.97±0.82	4.863±0.12	9.00±0.12	4.239±0.01	0.725±0.06	98.438±0.22
F12	600.1±0.55	4.946±0.16	8.25±0.58	4.253±0.06	0.779±0.01	98.402±0.35
F13	601.14±0.61	4.644±0.18	9.20±0.05	4.204±0.12	0.623±0.01	94.313±0.10
F14	600.5±0.62	4.943±0.12	9.12±0.44	4.144±0.02	0.542±0.05	99.504±0.47
F15	595.6±0.22	4.856±0.02	9.25±0.52	4.226±0.05	0.719±0.01	98.624±0.81
F16	598.6±0.21	4.226±0.11	9.25±0.57	4.226±0.05	0.712±0.01	99.024±0.87

All thevalues are expressed as mean± SD. (n=3)

Table no.5: Floating Lag Time & Total Floating Time of the formulations.

Formulation code	Floating Lag Time (sec)	Total Floating Time (hrs)
F1	110	>12
F2	138	>12
F3	174	>12
F4	116	>12
F5	135	>12
F6	146	>12
F7	126	>12
-F8	154	>12
F9	190	>12
F10	148	>12
F11	162	>12

F12	194	>12
F13	190	>12
F14	162	>12
F15	146	>12
F16	280	>12

***IN-VITRO*DRUGRELEASESTUDIES:**

Table no.6: *In-vitro* drug releasedata of Atazanavir floatingtablets F1-F9:

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	19.27±0.22	13.12±0.10	10.89±0.14	21.02±0.09	15.5±054	12.04±0.21	21.99±0.32	16.99±0.10	9.52±0.14
2	35.47±0.71	28.62±0.22	23.26±0.12	26.02±0.11	24.95±.91	18.91±0.25	38.87±0.11	24.01±0.24	17.47±0.37
3	48.53±0.21	37.21±0.34	35.62±0.08	35.57±0.44	27.27±0.70	26.63±0.11	49.61±0.46	33.89±0.38	25.32±0.32
4	56.75±0.65	42.35±0.12	46.26±0.65	46.36±0.81	35.17±0.90	36.46±0.66	53.14±0.42	38.82±0.38	37.34±0.09
5	73.83±0.21	56.39±0,33	55.41±0.42	88.82±0.36	44.03±0.54	38.54±0.76	59.38±0.39	45.85±0.17	41.62±0.28
6	85.96±0.35	65.85±0.46	69.32±0.15	63.77±0.83	52.93±0.75	49.08±0.92	67.17±0.52	55.83±0.27	55.63±0.56
7	97.11±0.22	78.19±0.78	75.87±0.24	76.42±0.64	59.07±0.38	59.03±0.86	74.95±0.99	68.72±0.84	63.85±0.14
8		83.92±0.43	86.51±0.65	85.41±0.30	68.26±0.53	67.10±0.26	85.43±0.67	75.29±0.20	79.28±0.73
9		97.64±0.50	92.35±0.25	99.26±0.69	74.19±0.53	68.30±0.75	97.82±0.32	86.14±0.54	87.63±0.12
10			99.86±0.60		97.93±0.10	77.40±0.86		99.68±0.43	94.48±0.54
11						98.65±0.45			99.40±0.86
12									

All thevalues are expressed as mean± SD. (n=3)

Table no.7: *In-vitro* drug released data of Atazanavir floatingtabletsof BatchF10 to F16:

Time	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0
1	9.26±0.23	8.12±0.04	7.89±0.11	26.98±0.17	15.05±0.12	10.04±0.24	5.26±0.05
2	25.47±0.20	15.62±0.11	13.26±0.18	35.02±0.30	24.95±0.09	18.91 ±0.14	11.91±0.22
3	38.53±0.34	27.21±0.17	25.62±0.37	41.57±0.26	27.27±0.63	26.63 ±0.64	20.63 ±0.65
4	46.75±0.56	32.35±0.68	36.26±0.13	48.36±0.76	35.17±0.32	36.46 ±0.65	26.46 ±0.60
5	53.83±0.72	46.39±0.61	45.41±0.28	54.82±0.52	44.03±0.16	42.54±0.43	33.54±0.76
6	65.96±0.23	55.85±0.03	59.32±0.02	59.77±0.53	52.93±0.12	49.08 ±0.76	48.08±0.67
7	77.11±0.66	68.19±0.14	65.87±0.12	66.42±0.25	61.07±0.48	56.03 ±0.34	57.03±0.13
8	88.98±0.43	75.92±0.42	76.51±0.17	74.41±0.96	70.26±0.37	62.10 ±0.64	64.10±0.54
9	99.64±0.32	88.64±0.76	87.35±0.24	83.92±0.82	83.19±0.87	69.30 ±0.21	69.30±0.20
10		98.23±0.26	92.62±0.10	87.72±0.90	89.93±0.59	75.40 ±0.78	75.40±0.40
11			99.86±0.54	96.35±0.43	92.73±0.64	86.95 ±0.45	81.95 ±0.84
12				102.98±0.32	98.54±0.52	92.81 ±0.18	85.62±0.80

***In-vitro*drugreleaseprofileofAtazanavir floatingtabletsof batches:**

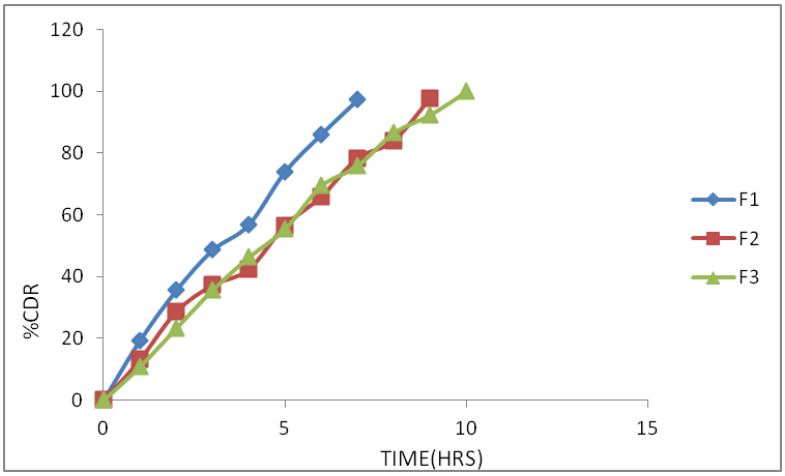


Figure no.9: % CDR OF F1-F3

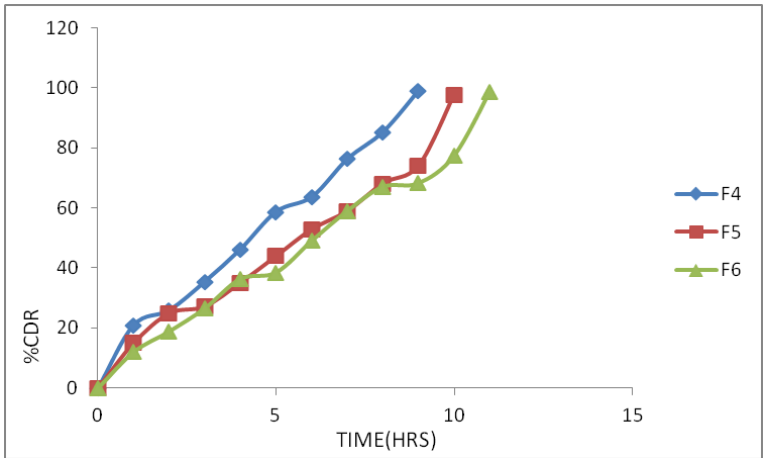


Figure mo.10:% CDR OF F4-F6

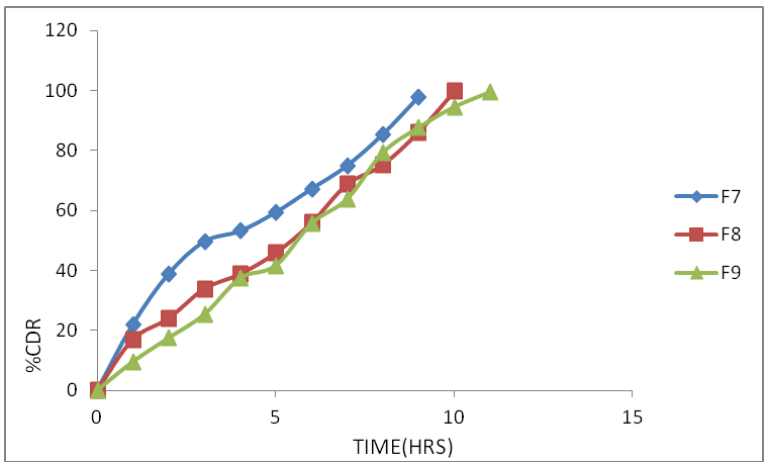


Figure no.11: % CDR OF F7-F9

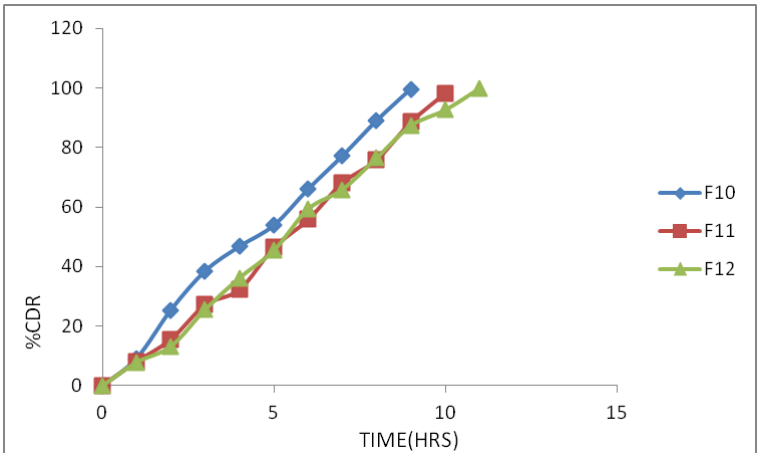


Figure no.12: % CDR OF F10-F12

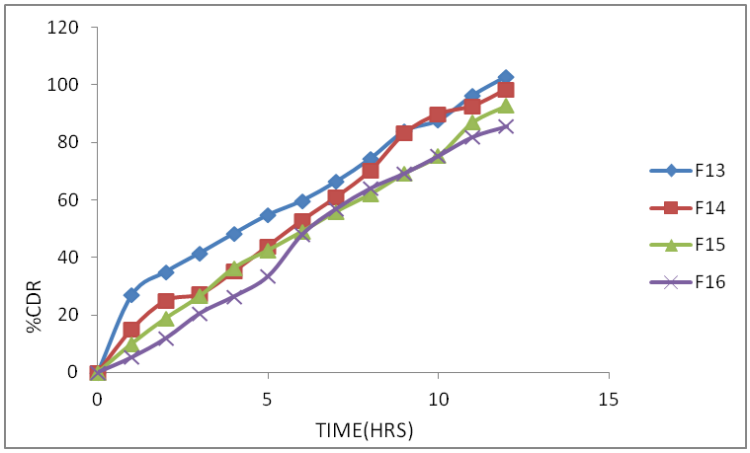


Figure no.13: % CDR OF F13-F16

ZERO ORDER:

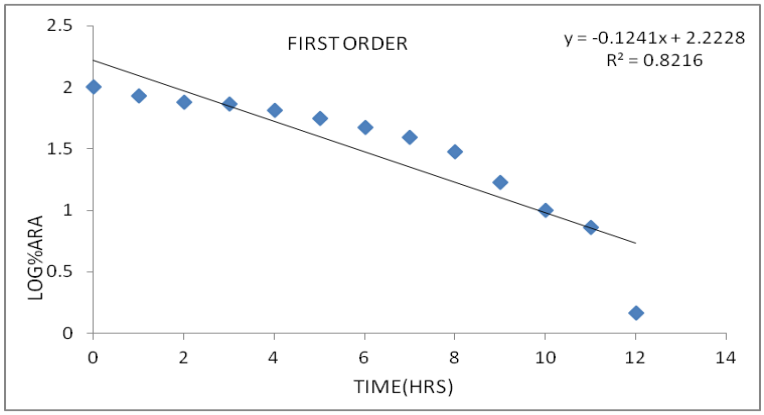
Time	%CDR
0	0
1	15.05
2	24.95
3	27.27
4	35.17
5	44.03
6	52.93
7	61.07
8	70.26
9	83.19
10	89.93
11	92.73
12	98.54

ZERO ORDER: (F14)

FIRST ORDER:

Time	LOG%ARA
0	2
1	1.929163
2	1.875351
3	1.861714
4	1.811776
5	1.747955
6	1.672744
7	1.590284
8	1.473341
9	1.225568
10	1.003029
11	0.861534
12	0.164353

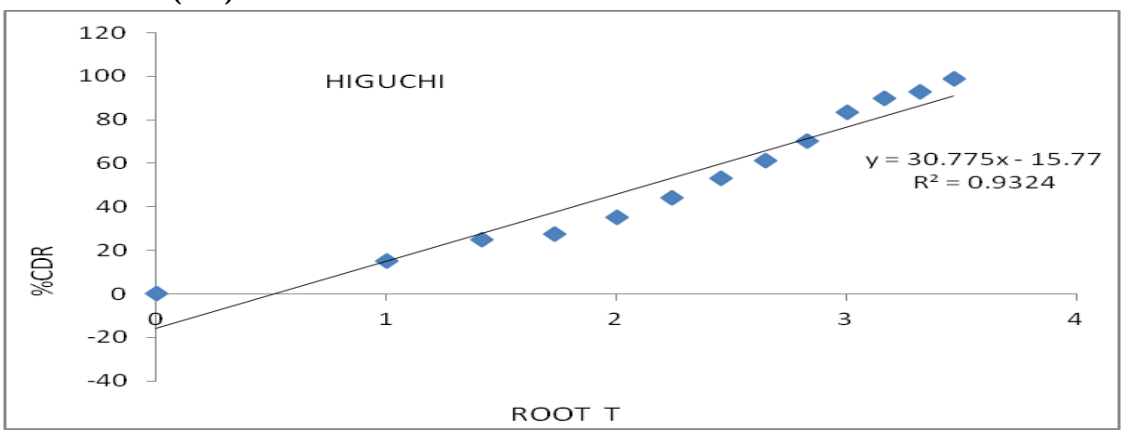
FIRST ORDER: (F14)



HIGUCHI PLOT:

ROOT T	%CDR
0	0
1	15.05
1.414214	24.95
1.732051	27.27
2	35.17
2.236068	44.03
2.44949	52.93
2.645751	61.07
2.828427	70.26
3	83.19
3.162278	89.93
3.316625	92.73
3.464102	98.54

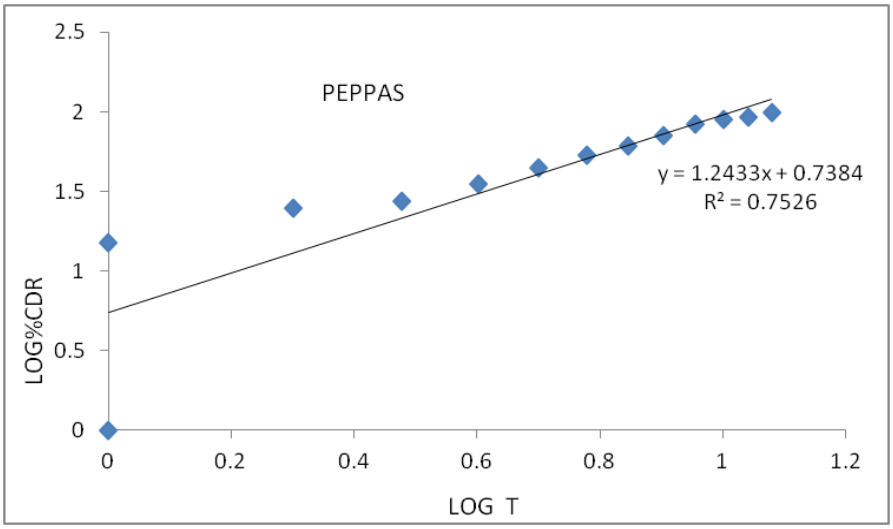
HIGUCHI PLOT: (F14)



PEPPAS PLOT

LOG T	LOG%CDR
#NUM!	#NUM!
0	1.177536
0.30103	1.397071
0.477121	1.435685
0.60206	1.546172
0.69897	1.643749
0.778151	1.723702
0.845098	1.785828
0.90309	1.846708
0.954243	1.920071
1	1.953905
1.041393	1.96722
1.079181	1.993613

PEPPAS PLOT: (F14)



RELEASE KINETICS: (F14)

REGRESSION VALUES	ZERO ORDER	FIRST ORDER	HIGUCHI PLOT	PEPPAS PLOT	n VALUE
R value	**0.991**	**0.821**	**0.932**	**0.752**	**1.243**

From the drug release kinetics it was concluded that the optimized formulation F14 follows zero order drug release and the n value indicates super caseII transport mechanism.

At(62sec)

Figure no.18: *In-vitro buoyancy* studies of the Atazanavir floatingtablet using guar gum (F14)

IV. DISCUSSION:

PREFORMULATION STUDIES:

- **Determination of melting point:**The melting point of Atazanavir was observed to be 209°C.
- **Determination of (λ) max of Atazanavir:** On the premise of preparatory distinguishing proof test it was inferred that the Atazanavir agreed the preparatory recognizable proof. By filtering the medication in U.V spectrophotometer in 200-400 nm extend, a sharp pinnacle was seen at 279nm utilizing 0.1NHCL as dissolvable. It was reasoned that the medication has λ max 279nm (according to I.P) as appeared in fig 9.
- **Preparation of the standard calibration curve of Atazanavir:** From the standard curve of Atazanavir it was watched that the medication complies with Beer's law in the range 2-12 µg/ml and the condition was produced.
- **Drug-polymer interaction study:** This was performed utilizing FTIR (KBr pellet strategy) **FTIR:** FTIR medicate polymers cooperation contemplates are appeared in fig 10-11.It was discovered that Atazanavir was perfect with the polymers utilized, there were no additional pinnacles saw in the improved definition when contrasted and the unadulterated medication. In this way the picked polymers for the details were observed to be perfect with Atazanavir and have no physical connection.

PRE-COMPRESSION EVALUATION PARAMETERS:
The angle of repose of the drug powder was in the range of 21.54 to 24.21, the Carr's index was found to be in the range of 11.53 to 17.29 indicating compressibility of the tablet. Haunser's ratio was found in the range of 1.10 to1.21is good as reported in table 6.

POST-COMPRESSION PARAMETERS:
Weight variation: Arranged tablets were assessed for weight variety and rate deviations from the normal weight are accounted for in table 7 and was observed to be inside the endorsed official points of confinement.

Friability: The friability of the definitions as observed to be between 0.54 to 0.77 is accounted for in table 5.5 and as that of which was observed to be inside the cutoff points of authority prerequisites (i.e. not over 1%).

Tablet density and hardness: The density of the tablet demonstrates the uniformity of bite the dust fill. The density of the tablet relies on the extent of the punch and the heaviness of the tablet (600mg). The density of the group from F1-F16 was observed to be 3.14-4.94 mm and hardness was observed to be 4.35-4.94 Kg/cm2 as detailed in table 7 which had great mechanical quality.

Drug content uniformity: The level of drug content for F1 to F16 was observed to be 94.313±0.10 to 99.504±0.47 of Atazanavir, it conforms to official determinations.

***In-vitro* buoyancy study:** Upon inundation in 0.1NHCL arrangement pH (1.2) at 370C , the tablets glided ,and remained light with no disintegration .From the outcomes it can be reasoned that the clump containing guar gum polymer indicated great floating lag time (FLT).

In-vitro dissolution studies: In-vitro dissolution studies were performed for all the clumps of tablets containing Atazanavir using USP XXIII dissolution test mechanical assembly II at 50rpm, 900ml of 0.1NHCl utilized as dissolution media.

By comparing the dissolution studies it was watched that the drug release from the definitions were observed to be F1 containing xanthan gum(15mg) demonstrates drug release of 97.11% drug release toward the finish of 7 hrs, so the centralization of the thickener was increased to get the sustained drug release, plan F2 containing thickener (30mg) indicates 97.64% drug release toward the finish of 9hrs, indicating that the drug release was not in a sustained way so the thickener fixation was increased to 45 mg in F3 detailing it indicates drug release in 98.94% toward the finish of 10 hours. where asformulationF4 containing karaya gum (15mg) demonstrates drug release of 99.26% drug release toward the finish of 9 hrs, so the convergence of the karaya gum was increased to get the sustained drug release, detailing F5 containing karaya gum (30mg) indicates 97.93% drug release toward the finish of 10 hours, indicating that the drug release was not in a sustained way so the karaya gum fixation was increased to 45 mg in F6 definition it demonstrates drug release in 98.65% toward the finish of 11hours.

Whereas detailing F7 containing guar gum (15mg) demonstrates drug release of 97.82% drug release toward the finish of 7 hrs, so the grouping of the guar gum was increased to getthe sustained drug release, plan F8 containing guar gum (30mg) indicates 97.82% drug release toward the finish of 8hrs, indicating that the drug release was not in a sustained way so the karaya gum focus was increased to 45 mg in F9 definition it demonstrates drug release in 99.40% toward the finish of 11 hours.

Whereas definition F10 containing carbopol (15mg) demonstrates drug release of 99.64% drug release toward the finish of 9 hours, so the convergence of the guar gum was increased to get the sustained drug release, detailing F11 containing carbopol (30mg) indicates 98.23% drug release toward the finish of 10hours, indicating that the drug release was not in a sustained way so the carbopol focus was increased to 45 mg in F12 plan it indicates drug release in 99.86% toward the finish of 11 hours..

By observing the drug release examples of plans F1-F12 it was distinguished that the drug release was not in a sustained way. So the centralizations of the polymers were increased to 60mg to get the sustained drug release.

By this it was inferred that the polymer containing guar gum 60mg shows sustained drug release toward the finish of 12hours by 98.54% drug release. So the drug release kinetics were performed for F14 definition containing guar gum 60mg.

Drug release kinetics: The in-vitro drug release information was subjected to examination according to zero request and the first arrange kinetic conditions, Higuchi and Peppas models to as certain the instrument of drug release. The consequences of the line a relapse examination of information including relapse coefficient are outlined in table 8.

From the drug release kinetics it was presumed that the upgraded plan F14 takes after zero request drug release and the n esteem indicates super case II transport instrument.

V. CONCLUSION:

From the compatibility studies, it can be reasoned that, xanthan gum, guar gum karaya gum and carbopol were suitable and compatible with drug Atazanavir and in this way appropriate for the formulation of Atazanavir floating tablets.

Atazanavir tablets were prepared by direct compression technique.

In-vitro buoyancy studies were performed for each one of them, F1toF16 with utilization of *0.1NHCL arrangement at37℃. Tablet containing guar gum (F14) demonstrated good buoyancy with short lag time and long buoyancy time of over 12 hours in 0.1NHCL. In-Vitro release studies were conducted for 12hours. Upgraded formula containing guar gum (F14) demonstrated better release contrast with different details and it took after zero release kinetics and shows super case II transport.

From this examination, it was inferred that guar gum can be utilized as a part of formulation of Atazanavir sustained release gastro retentive floating drug delivery system. Overall, this investigation reasons that consistency of the polymer (viscosity) is a main consideration factor affecting the drug release and floating properties of FDDS.

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